Bone Marrow Imaging

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(1) Background

Bone marrow is the body's 4th largest organ constituting 5% of its body weight. It consists of trabecular bone and a variety of cells including hematopoetic, fat, stroma and RES cells as well as sinsusoids. Bone marrow composition changes with age, which is reflected in a change in signal characteristics in MR images. Red marrow, which is found in younger individuals is composed of 40% fat and 40% water while yellow bone marrow contains approximately 80% fat and 15% water. MRI is an extremely sensitive technique to detect bone marrow pathology. However, in order to correctly assess its pathology we should be aware of its normal age-related morphology as well as reactive physiological changes. It should also be considered that problems may occur if bone marrow infiltration is diffuse and differentiation of hematopoietic bone marrow and neoplastic infiltration may sometimes be difficult.

(2) Standard Imaging Techniques

Standard sequences for bone marrow pathology include T1-weighted spin-echo (SE), STIR (short TI inversion recovery sequences) or T2-weighted fat saturated fast SE sequences. T1-weighted sequences are very useful for initial evaluation as signal of muscle and intervertebral disc may be applied for internal calibration: bone marrow that is lower in signal than muscle and disc is considered as pathological. STIR sequences are very sensitive in detecting bone marrow edema or hypercellular bone marrow, but it should be considered that theses findings may not be very specific. In T2-weighted fast SE sequences a radiofrequency pulse is used for spectral selective fat saturation; these depict anatomical structures usually better than STIR sequences yet with larger field of views or metal fat suppression tends to be inhomogeneous. Contrast enhanced sequences may add information, for example in better assessing intraspinal pathology or soft tissue extension of lesions, but application is discussed controversially. Important applications of Gd-based contrast media include (1) differentiation of cystic and solid bone marrow lesion, (2) differentiation of viable and necrotic tissue to guide biopsy, (3) abscess versus solid tissue in infection and (4) monitoring of therapy response in tumor and infection.

MR techniques have evolved substantially and extensive coverage of the skeleton is possible with good image quality and within a reasonable acquisition time. For whole body imaging moving table techniques and whole body coils have been described. Whole body MR imaging of the skeleton is more sensitive than skeletal scintigraphy in detecting neoplastic bone marrow pathology (1).

(3) Normal Bone Marrow

In evaluating MR images one has to be aware of signal characteristics of normal bone marrow: in young patients substantial amounts of hematopoietic bone marrow are found and below the age of 10 years in T1-weighted images the bone marrow may be lower in signal intensity than surrounding muscle or intervertebral disc (2) (Fig. 1). Above the age of 10 years lower signal intensity is considered as pathological. Conversion from hematopoietic to fatty bone marrow starts in the periphery and the distal part of the long bones. By the age of 20 years most of the appendicular skeleton contains fatty bone marrow, while the central skeleton including proximal femur and humerus contain largely hematopoietic bone marrow. In the 6th decade of life a substantial amount of fatty bone marrow is also found in the axial skeleton. Please note also that reconversion of fatty to hematopoietic bone marrow may be observed, associated for example with status post chemotherapy, obesity, pulmonal pathology, smoking and marathon running.

Hematopoietic bone marrow is an important MRI *differential diagnosis* in myeloproliferative disorders and sometimes is very difficult to differentiate from neoplastic disease in patients with malignancies. However, in MR images hematopoietic bone marrow is usually not geographic and more vague in appearance, it is frequently symmetric and located in the metaphyses, the signal is brighter than that of muscle in T1-weighted sequences and both bone scan and FDG PET are negative. Bone marrow metastases are frequently more focal and rarely diffuse.

Fig. 1: Normal bone marrow in a 12 months old child, T1-weighted SE sequences: sagittal image of the thoracic and cervical spine (left) and coronal image of the femur (right). The bone marrow in the vertebrae is lower than that of the discs. In the coronal image of the femur the signal of the bone marrow in the diaphysis is lower than that of the surrounding muscles.
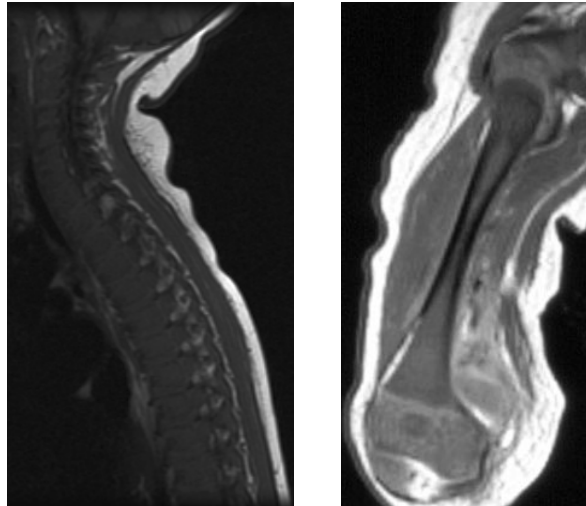
(4) Pathologies and Imaging characteristics
4.1. Myeloproliferative disorders

Myeloproliferative disorders are a group of diseases that cause an overproduction of bone marrow cells such as platelets, white blood cells, and red blood cells. These include myelofibrosis, polycythemia vera, chronic and acute leukemias and primary thrombocythemia. Multiple myeloma is the most common neoplastic disease of the bone marrow.

Predominantly fibrotic bone marrow pathology

In *myelofibrosis* polyclonal activation of fibroblasts occurs which secrete collagen, causing fibrosis. This results in extramedullary hematopoesis in liver and spleen and immature blood cells in the peripheral blood. In *myelofibrosis* the predominant radiographic feature is osteosclerosis that may be found in 30-70% of the patients and it is most evident in the bones of the axial skeleton in particular spine and pelvis (3). MRI is very sensitive in assessing the extent of the disease; low signal intensity changes both in T1- and T2-weighted images are shown, due to replacement of marrow fat by collagen and reticulin fibers (Fig. 2). Note however, that these signal changes may also be found in children with leukemia and Gaucher's disease as well as in iron overload (chronic hemolysis, thalassemia) and AIDS (3). Differentiation of myelofibrosis may also be difficult from osteoblastic, metastatic disease if no radiographs are available.

Fig. 2: Sagittal T1-weighted (left) and fat-saturated T2-weighted (right) FSE sequences of the lumbar spine in a patient with myelofibrosis. Note low signal intensity of the bone marrow in both T1- and T2-weighted imaging sequences. In the T1-weighted sequences the signal intensity of the bone marrow is similar as this of the discs.

Predominantly hypercellular bone marrow pathology

In *polycythemia vera* an increase in all three cell types is found which results in pancytosis with normal differential and high hematocrit. In *CML* substantial leukocytosis (> 20.000/ml) with too many myelocytes is found and leukocyte alkaline phosphatase is decreased. *Acute myelogenous leukemia* (AML) is the most frequent leukemia found in adulthood and has a number of different subtypes. Auer rods and discrete tumor masses infiltrating the soft tissues are typical findings. *Acute lymphoblastic leukemia* (ALL) is the most common childhood malignancy; B-cell, T-cell and null cell ALL are differentiated, B-cell ALL has a better prognosis. Positive stain for periodic acid schiff's (PAS) and negative myeloperoxidase stain are typically found in ALL. Idiopathic *thrombocythemia* is a rare malignant disease with megakaryocytes that have a bizarre morphology and platelet counts of more than 1 million/ml.

Multiple myeloma (MM) is a clonal B-lymphocyte neoplasm and the most frequent primary malignancy of the bone marrow, accounting for 10% of hematologic malignancies. It is usually systemic, but solitary osseous myeloma is found in approximately 5% of the cases and frequently these tumors progress to MM. Serum protein electrophoresis reveals monoclonal spikes due to gammopathy and Bence-Jones proteins are a typical finding in the urine. Lytic lesions found in the bone are due to an osteoclast-activating factor that is produced by the tumor cells. Amyloidosis and light-

chain cast nephropathy are additional characteristic findings. Histologically sheets of plasma cells are found in the bone marrow.

Mastocytosis respectively mast cell disease is characterized by the abnormal growth and accumulation of neoplastic mast cells within the bone or other organs. The diagnosis of systemic mastocytosis is most commonly established by a thorough histological and immunohistochemical examination of a bone marrow trephine specimen.

There are *three patterns of pathological MR patterns in these predominantly hypercellular myeloproliferative disorders*: (i) a focal pattern with localized areas of abnormal marrow, these focal lesions are low in signal in T1-weighted images, bright in fat-saturated T2-weighted images and show contrast enhancement, this pattern is found in multiple myeloma and lymphomas, but is most typical for metastatic disease from solid primary malignancies. (ii) The diffuse pattern shows replacement of the normal marrow with intervertebral discs and muscle appearing in T1-weighted sequences similar or higher in signal than the bone marrow. The bone marrow is bright in fat saturated T2-weighted or STIR sequences and shows substantial contrast enhancement. Depending on the degree of diffuse bone marrow infiltration, however, diagnosis may be difficult and if less than 20% of the bone marrow is diffusely infiltrated it is not possible to differentiate malignant infiltration with confidence from hematopoietic bone marrow (4). The diffuse pattern of disease is found in acute leukemias but may also be found in multiple myeloma and other myeloproliferative diseases. (iii) The variegated pattern consists of multiple, innumerable, small foci of disease on a background of normal bone marrow (Fig. 3). These foci are low in signal intensity in T1-weighted images, bright in T2-weighted images and enhance after contrast administration. If no fat saturation is used the lesions may be masked by contrast medium in T1-weighted images. The variegated pattern is typically found in multiple myeloma.

Fig. 3: Coronal T1-weighted SE image in a patient with multiple myeloma. Diffuse bone marrow infiltration is shown with a variegated pattern in the pelvic bones, the lumbar spine and bilateral proximal femur.
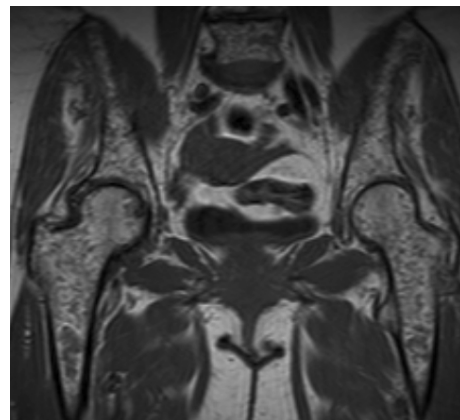
In *acute leukemias* a diffuse MR pattern is typical but not very specific. MRI is sensitive in depicting bone marrow infiltration but has a poor specificity in differentiating active disease from post treatment changes in AML, yet may better predict response in ALL (5). MRI may also help in differentiating tumor involvement (such as chloromas) from complications of the disease (such as osteomyelitis).

Other myeloproliferative disorders such as *CML, polycythemia vera and thrombocythemia* may have similar imaging findings, which are non specific and may only have a limited role in staging the disease or determining prognostic outcome.

Multiple myeloma is one of the most frequent hematological malignancies. As compared to the variegated pattern (Fig. 3), diffuse or focal marrow involvement tend to have a higher tumor burden (6). The focal pattern is most frequently seen, while a diffuse pattern is seen in 25% of the patients. After treatment bone marrow changes may resolve, but may also be unchanged, even if patients achieve complete remission. Sometimes changes in the enhancement pattern may be shown or transformation of a diffuse into variegated or focal pattern may be found (5). Progression of vertebral compression fractures also does not necessarily suggest disease progression but may be due to collapse of the unsupported vertebra. MRI has an important role in assessing extraosseous masses and neurologic involvement of the disease, such as infiltration of the spinal canal.

Lymphoproliferative disorders are divided into Hodgkin's and non-Hodgkin's lymphomas and infiltration of the bone marrow is found in 5-15% of patients with Hodgkin's and 20-40% of patients with non-Hodgkin's disease (5). MRI may show the infiltration more sensitively than bone marrow scintigraphy but may be less accurate than FDG PET in assessing therapy response. On T1-weighted MR images involvement is usually more diffuse or heterogeneous and less frequently focal. These MR findings are not typical for this disease entity and may be found in other myeloproliferative disease too. A soft tissue mass around an apparent intact cortical bone, however, raises concern for lymphoma, though it may be found in small cell malignancies too.

4.2. Secondary neoplasias

Metastases are the most frequent malignancies in the bone marrow and usually they are focal as described in the previous chapter. Whole body MRI is very sensitive in detecting these lesions, and has a superior sensitivity compared to bone and bone marrow scintigraphy (1, 7). T1-weighted SE or STIR sequences usually are well suited for bone marrow imaging in patients with suspected metastases. It should be noted that metastases may not be sufficiently visualized with contrast-enhanced T1-weighted sequences as they may the same signal as the surrounding bone marrow. With additional fat saturation, however, neoplastic lesions are sensitively detected. Since sclerotic metastases may have atypical signal patterns and are sometimes not well visualized with STIR sequences MR-findings should always be correlated with radiographs.

One of the most challenging *differential diagnoses* in pathologic compression fractures are insufficiency fractures due to osteoporosis. In patients with *osteoporotic compression fractures* the bone marrow signal may be normal, if fractures are old, in subacute and acute fracture the bone marrow signal may be abnormal but usually extends parallel to the endplate and does not involve the whole vertebra. The posterior border of fractured vertebrae in osteoporosis is usually concave and not convex and signal abnormalities do not typically extend into the pedicles.

4.3. Diseases with reduced numbers of bone marrow cells

In aplastic anemia the bone marrow is extremely hypoplastic and may exhibit less than 30% residual hematopoetic cells on histological exam obtained after bone marrow biopsy. Increased signal intensity in T1-weighted images is found and is due to fat cell

proliferation. Areas of fibrosis may also be visualized and in more advanced stages bone marrow infarction/ avascular necrosis may be demonstrated.

Other conditions that are associated with hypoplastic, fatty bone marrow are status post radiation and chemotherapy (Fig. 4). Bone marrow cell depletion may also be found associated with AIDS and may be due to the virus or therapy induced. Myelofibrosis was described in detail in chapter 4.1.

Fig. 4: Bone marrow before and after chemotherapy. Coronal T1-weighted MR images of the pelvis before (left) and after (right) chemotherapy for a pelvic soft tissue sarcoma (arrows). As the tumor size shrinks increasing depletion of bone marrow cells is found.
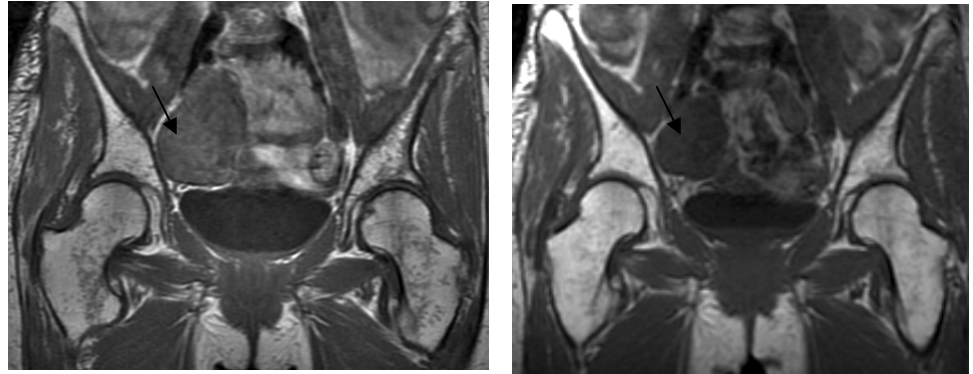

4.4. Hemoglobinopathies

Sickle cell disease is found in approximately 0.15% of African-American children and leads to small vessel occlusion and hemolytic anemia in particular with decreased oxygen tension. In the bone marrow an increased amount of hematopoetic cells is demonstrated and bone marrow infarction is a typical finding. The increased amount of red bone marrow goes along with diffusely low signal intensity lesions in the T1-weighted sequences and increased signal in STIR sequences. Bone marrow infarction has more complex signal changes due to necrosis, fatty degeneration and granulation tissue.

In thalassemia a defect of hemoglobin subunits is found leading to anemia. This anemia causes an increase in hematopoetic bone marrow, which sometimes can cause substantial expansion of bone marrow space and tumor-like extramedullary hematopoesis.

4.5. Bone marrow storage disease

Gaucher's disease is a metabolic storage disorder due a defect of the enzyme glucocerebrosidase. This leads to progressive proliferation of Gaucher cells with accumulated undegraded glycolipids, resulting in expansion of the marrow space (Erlenmeyer flask deformity), bone erosion with an increased number of fractures and infarction of the bone marrow. The Gaucher cells have low signal intensity both in T1- and T2-weighted sequences (Fig. 5). Bone marrow infiltration starts proximal and increasingly affects more peripheral areas of the appendicular skeleton. Bone marrow infarction is also a typical finding related to Gaucher' s disease and is characterized by a more serpiginous pattern with bright signal in fat saturated T2-weighted or STIR sequences (Fig. 5).

Fig. 5: Gaucher's disease. Coronal T1-weighted (left) and STIR (right) sequences. Areas of bright signal in STIR image correlate to bone infarction and areas with low signal intensity in both T1-weighted and STIR image are consistent with Gaucher cell infiltration. Please note metal artifacts at the right distal femur due to previous fracture and internal fixation.
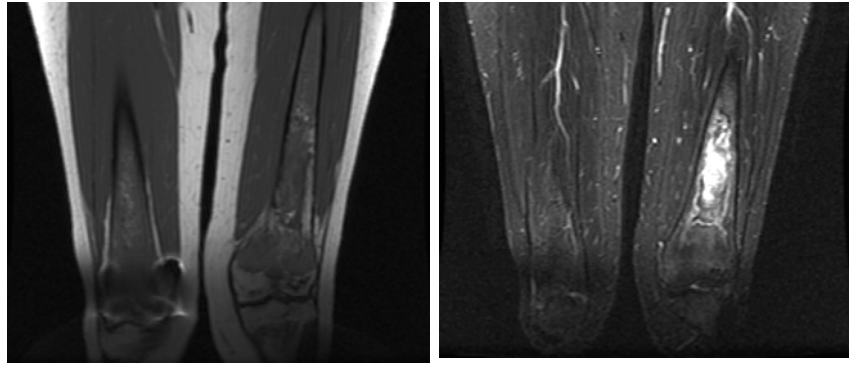
Secondary hemochromatosis may be due to repeated blood transfusions and leads to diffusely low signal intensity of the bone marrow in both T1- and T2-weighted sequences. Please note that primary hemochromatosis usually does not affect MR morphology of bone marrow.

4.5. Increased vascularity of bone marrow

Increased vascularity of bone marrow may be due to infection or tumor. MRI is well suited to assess activity of infection. Monitoring of tumor response with MRI may be more challenging. As tumor cells are decreasing in number, granulation tissue will proliferate which has similar signal intensity and contrast enhancement pattern compared to active tumor tissue. In these cases FDG-PET may be more sensitive in diagnosing active tumor tissue.

Decreased vascularity of bone marrow is found in avascular necrosis and bone marrow infarction. Avascular necrosis is most frequent in the femur head and may be idiopathic or due to corticosteroids, chemotherapy and trauma. Usually the necrotic area undergoes fatty degeneration and is surrounded by a rim of granulation tissue. In early stages a substantial amount of edema may be found. It should be noted that due to the increased extravascular space edema also shows (delayed) contrast enhancement after Gd-based contrast media application. Thus this enhancement may not necessarily be due to viability of the tissue. If there is, however, no contrast enhancement of the tissue necrosis is expected.

(5) Advanced Imaging Techniques and Future Developments

Differentiation of compression fractures due to malignancy or osteoporosis may be difficult. Diffusion weighted (DW) imaging has been described useful in the differential diagnosis (8, 9). Acute benign osteoporotic fractures show hypo- or isointense signal on DW sequences that reflects persistent free water proton mobility. With increasing diffusion strength a substantial signal loss is found. Metastatic fractures show hyperintensity compared with normal surrounding bone marrow probably due to altered water proton mobility within neoplasm.

Differentiation of hematopoetic bone marrow and neoplastic disease sometimes is a substantial problem and standard MR techniques are limited in their diagnostic performance. Ultrasmall superparamagnetic iron oxides (USPIOS) are a new iron based

contrast agent, which is phagocytosed by normal reticuloendothelial cells in the hematopoetic bone marrow but not by neoplastic tumor deposits within the bone marrow. Its potential to differentiate normal and neoplastic bone marrow and to increase the bone marrow-to-tumor contrast has been shown in a previous study (10).

(6) Conclusion and summary

Imaging characteristics of normal bone marrow change through life and familiarity with these changes is important to correctly approach bone marrow pathology. Neoplastic disease of the bone marrow is a frequent pathology and may have different morphologic patterns. A number of bone marrow pathologies are characterized by a depletion of normal hematopoetic bone marrow cells. Storage diseases and hemoglobinopathies may have typical bone marrow patterns, which are well visualized with MRI. A number of pathologies may go along with increased or decreased vascularity of bone marrow. While standard imaging of bone marrow is based on a few standard sequences (in particular T1-weighted and STIR sequences) new techniques are being developed to better characterize certain pathologic conditions.

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